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SUMMARY: The growth of pulmonary function between 5.5 and 25 yr of age was determined using 1,511 observations over time on 353 subjects from a representative population sample of white non-Mexican-Americans in Tucson. There was an average of 8.8 yr of follow-up, with a maximum of 12. The method used was shown to be robust for span of follow-up from 3 to 12 yr (3 to 7 observations), and the results were verified by standard statistical methods. The standard error of the estimate decreased linearly with follow-up, indicating th eneed for longitudinal evaluation. Respiratory symptoms and diagnoses had the biggest negative impact on growth of lung function, using FVC, FEV1, Vmax50, and size-compensated flows (Vmax50/FVC). Smoking had the next biggest negative impact. Smoking cessation was shown to have a positive impact on growth of pulmonary function. Using a second linear model to adjust for individual variability and the random variability over surveys, individual growth showed similar trends. Further negative impacts were due to parental smoking, especially as it interacts with active smoking and respiratory disease. Flows at end of follow-up (Vmax50, Vmax50/FVC) were more sensitive than FEV1 to the effects of concurrent disease and smoking, and more persistent effects of these factors in early adulthood.

Longitudinal Study of Pulmonary Function Development in Childhood, Adolescence, and Early Adulthood

Development of Pulmonary Function[1-4]

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Introduction

The study of the growth of pulmonary function in childhood and into early adulthood has stimulated many investigations. Although there have been various evaluations of this "growth" cross-sectionally, fewer studies have evaluated such growth through longitudinal measurements of pulmonary function (1-9). Many of these studies have been with only 2 observations over time. For those studies with 3 or more points in time, the basic questions relate to how to represent the generalized growth model, how growth is statistically dependent on initial measures of function, how it is related to respiratory illnesses in childhood, and the effects of active smoking, passive smoking, and other environmental factors. Basic questions are whether there are differences in growth between the 2 sexes (10), and whether airways of different sizes grow at the same rate or are affected differently by internal and external factors (11).

This report evaluates the longitudinal growth of pulmonary function in subjects who have been enrolled in the Tucson Epidemiological Study of Airways Obstructive Diseases since 1972 (12). It is a study of the development of spirometric function and the characteristics and robustness of a model of growth. The effects of sex, age, size, and of other respiratory factors on growth are examined. The report attempts to evaluate the effects of initial function, symptoms, disease during childhood, the onset of smoking, parental symptoms and parental smoking.

Methods

Subjects studied were those enrolled in the longitudinal epidemiologic study of white non-Mexican-American households in Tucson. The study has been described in detail elsewhere (12).

Spirometric Testing Over Time

Subjects 5.5 yr of age or older were tested spirometrically with a pneumotachygraph, using ATS/Snowbird criteria, as described previously (13, 14). The measures of pulmonary function derived were FVC, FEV_1, flow at 50% of FVC ($\dot{V}max_{50}$), and flow at 75% of expired FVC ($\dot{V}max_{75}$). Their percent of predicted FEV_1 values were in the range of 49 to 151% at entry, using our previously published prediction formulas (14).

Subjects were tested in Surveys 1 to 8 (February 1972 through May 1984), with the exception of Survey 4. Thus, it was possible to have a maximum of 7 observations. We required at least 3 yr of follow-up for subjects to be included in the data file. There were a total of 1,511 observations on 353 subjects 5.5 to 15 yr of age at the time of their first satisfactory testing, and the oldest was 25 yr of age at the end of follow-up. The maximum length of follow-up was 12 yr, and the average was 8.8 yr; table 1 shows the 1,511 observations divided by the number of observations per person. The height distribution by age appeared normal for a pediatric population.

The age range was divided into four 5-yr intervals to evaluate cohort effects; cohorts were divided into those in an age group who had their first spirometric test either during the first 3 yr of the study (1972 to 1975) or whose first test was performed during subsequent surveys (1977 or later). Using multiple regression techniques, each pulmonary function variable was regressed against age (years, decimalized), height (in inches), and the 2 together, separately for those within each age group and by cohort. Differences were evaluated by multifactorial analyses of variance (ANOVA) as well, in which gender was a covariate. In these analyses, gender was not significant for $\dot{V}max_{50}$, and was inconsistent for FEV_1. There were no significant differences between cohorts in the specific regressions in the 4 age groups (5.5 to 10 yr, 11 to 15, 16 to 20, and 21 to 25), for any of the 4 measures (FVC, FEV_1, $\dot{V}max_{50}$, $\dot{V}max_{75}$), as confirmed by ANOVA. The $\dot{V}max_{75}$ results were highly variable, and were not used further. Thus, we studied all subjects with longitudinal data, regardless of when they entered the longitudinal study.

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TABLE 1

THE NUMBER OF OBSERVATIONS PER INDIVIDUAL SUBJECT

	2	3	4	5	6	7	Total
Observations							
n	56	210	440	425	240	140	1,511
%	3.7	13.9	29.1	28.1	15.9	9.3	100.0
Subjects							
n	28	70	110	85	40	20	353
%	7.9	19.8	31.2	24.1	11.3	5.7	100.0

The effect of multiple longitudinal observations per individual subject within the different age groups was evaluated to determine the possible dependence of multiple observations in the same subjects over time. Only 4.3% of those with 3 longitudinal observations were within the same age group. Those with 3 or more longitudinal observations had 56% of such observations in 2 different age groups, 41% in 3, and 2% in 4 different age groups. Thus, individual subjects tended to have observations spread throughout the age range. The number of observations was used as a covariate in later analyses to represent each subject's contribution to those analyses.

Method of Evaluating Functional Development

The first approach chosen for the present evaluation of development ("growth") was to use all observations of all subjects over the age range in the longitudinal data set to find the best-fitting equations (using least squares). It is similar to the descriptive approaches used previously in this study (15–18). This approach is generally one of using unweighted observations per individual to evaluate each pulmonary function variable. The best fitting composite equations were curvilinear, relating to age as well as to height. The robustness of the method was determined by comparing the values derived for subgroups with differing numbers of observations. The values for those with only 2 points differed significantly from those with 3 or more observations. Therefore, those subjects with only 2 points were excluded from further analysis. The standard error of the estimate for FEV_1 by number of observations for 3 or more points ranged from 0.3 to 0.5 L, and decreased with the number of observations; the multiple correlation coefficient increased with the number of observations from about 0.88 to 0.95 for FEV_1. Thus, predicted values fit the observed values very closely. The standard error of the estimate and the multiple correlation coefficient for the $\dot{V}max_{50}$ did not have any trend related to the number of observations.

Results of Composite Fitting

Forms of the equations and resulting predictions derived from each of the other longitudinal subsets defined by the number of observations were similar in appearance. Age (in decimalized years) and a height-height squared function (height in inches) were important overall and in all age groups. In females, height did not explain as much of variance in parameters as it did in males. Age squared was important for the curvilinear model of $\dot{V}max_{50}/FVC$ as well.

The FEV_1 and FVC were greater for males than for females, but were a relatively constant function of height at each age. Thus, these variables and the $\dot{V}max_{50}/FVC$ were evaluated using separate gender models (13, 14) and/or using sex as a covariable (9). Completely separate gender analyses did not contribute much useful information, and are not discussed at length.

The final curvilinear equations that best explain the development of function between 5 and 25 yr of age, based on 3 or more observations per subject, were derived for FVC and FEV_1 (in liters), $\dot{V}max_{50}$ (liters/second), and $\dot{V}max_{50}/FVC$ (in liters/FVC seconds, as a measure of lung size-compensated flows). They are as follows:

$$FVC = 9.17 + 0.054\,Age - 0.373\,Height + 0.004\,Height^2 \quad (SEE = 0.495,\ R = 0.923,\ p < 0.001).$$

$$FEV_1 = 6.844 + 0.040\,Age - 0.281\,Height + 0.003\,Height^2 \quad (SEE = 0.431,\ R = 0.916,\ p < 0.001).$$

$$\dot{V}max_{50} = 5.489 + 0.056\,Age - 0.221\,Height + 0.003\,Height^2 \quad (SEE = 1.037,\ R = 0.717,\ p < 0.001).$$

$$\dot{V}max_{50}/FVC = 4.65 + 0.070\,Age - 0.0019\,Age^2 - 0.116\,Height + 0.0008\,Height^2 \quad (SEE = 0.296,\ R = 0.278,\ p < 0.001).$$

Residuals

Residuals from the equations did not correlate with any further age, age-height, or size determinants (including sitting height and arm span). Average age did correlate with number of observations; those having the largest number of observations were an average of 1 yr younger than those having only 3 observations. This was not a factor that influenced the results.

To analyze differences related to other factors, residuals from the equations were derived for each observation and were expressed as proportions of the predicted values. Residuals are positive if above the predicted value and negative if below it; percent predicted can be calculated by adding 100% to the residual. The residuals thus derived were normally distributed within age groups and overall, and age was not a major factor in determining these distributions.

Residuals for observations of all subjects had significant autocorrelations with at least 3 prior observations of FEV_1 and $\dot{V}max_{50}$ when entered hierarchically in multiple regressions. The simple correlation for FEV_1 values in adjacent surveys was 0.77, decreasing to 0.53 for values 3 surveys apart. Therefore, because of autocorrelations, in most analyses we evaluated the effect of factors using only the end-point residuals for each individual subject, as representing that subject's outcome value.

In addition, end-point residuals were calculated for all subjects younger than 14 yr of age at entry with any spirometric test who were 12.4 to 26.4 yr of age at the time of their last spirometry (n = 440). This allowed us to assess effects of early respiratory illnesses and effects of early exposures to tobacco smoke on end-point function.

Statistical Comparisons

Statistical analyses were performed on the DEC 10-Cyber 175 of the University Computer Center, using the SPSS statistical package, the BMDP Package (19), and custom Fortran programs.

Methods used included those of previous studies, such as multifactor analysis of variance (ANOVA) and covariance (ANCOVA) (9), and more standard evaluations of subgroup differences (3, 5, 6, 8, 15–18). Age and sex were used as covariables, as in the analyses of Ware and coworkers (9), except when specified. Analyses evaluated the independent and interactive effects of various risk factors on lung function. As height is a function of age also, and as their effects on function are combined biologically between puberty and maximum lung growth (17), interactions of these 2 were used in these analyses. Because the method used is a variant of the repeated measures ANOVA (linear model) (19, 20), the repeated measures ANOVA model was used as well (19), in part to verify the results from the method and the multifactorial ANOVA and ANCOVA.

Individual Development Curve Model

A second major approach assessing relationships between other factors and the multiple cumulative change in function used individual development ("growth") functions of the term age times height^3 that best linearized the changes in lung function with time. This is the same term found to best describe the rate of change in adults in our study (18), and found previously with other descriptive methods (17). The interaction is important biologically, as explained above. For subjects with at least 3 data points, standard errors of estimate derived in the process were used as measures of individual variability in analyses of the slope using the approach of Goldstein (21, 22). In this approach, developmental ("growth rate") functions (or individual "slopes") are the dependent variables analyzed in generalized mixed linear models with covariables (age, sex, height), risk factors of

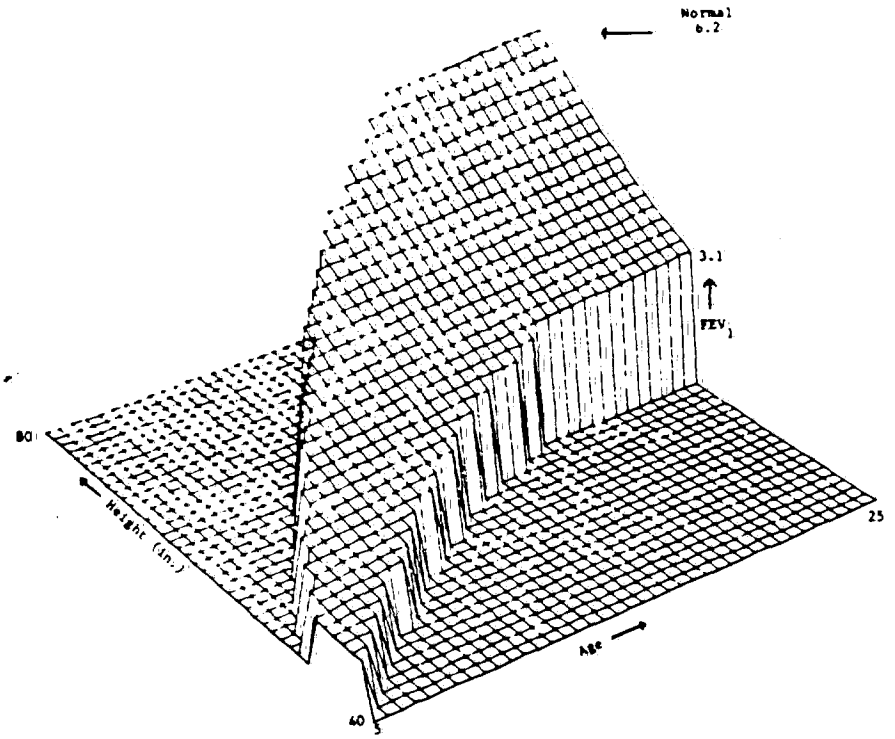

Fig 1. Predicted FEV, by age and height and symptom status (details and formulas in text).

interest, individual variability (as mentioned), numbers of observations (as mentioned), and years of follow-up. Hierarchical approaches were evaluated in these processes. One can then use variables representing change (in height, smoking, etc.) as independent variables.

Personal smoking and the standard airways obstructive disease (AOD) symptoms were derived from questionnaires completed over time by the subject or by the parent when the subject was younger than 15 yr of age (12, 14–18).

Results

The three-dimensional solution of the equation for the FEV_1 is shown in figure 1. It shows clearly the curvilinear relationship of function with age and height (and curvilinearity with both together). The three-dimensional solution was of the same form for asymptomatic nonsmokers ("normals") and for others. At age 25, the results for these "other" subjects shows an apparent deficit in FEV_1 of 200 to 300 ml, approximately 6% of normal function. The equation is of the same form for the 2 genders, differing only in age contribution. The only variable showing a meaningful age-sex interaction was $\dot{V}max_{50}/FVC$. These data are shown in figure 2.

Residuals of all pulmonary function variables were significantly related to significant AOD symptoms in all age groups; the most sensitive indicator was $\dot{V}max_{50}$ (table 2). Those who were asymptomatic had no significant variation of residuals of lung function with age. In contrast, most symptom groups showed variability over the age range. Those with cough appear to show an increasing loss of function with age. Asthma was related to the worst lung function in each age group.

Outcome pulmonary function was evaluated by the longitudinal status of physician-confirmed disease, specifically asthma or chronic bronchitis. Longitudinal status in those who entered the study as children (initial ages zero to 14) was considered constant (always or never), new, or remitted, as seen in table 3. Ever diagnosed asthma and chronic bronchitis had prevalence rates of 6.1 and 7.3%, respectively. About 45% of those with either diagnosis had both. Those who had physician-confirmed asthma or chronic bronchitis throughout the study had significantly lower outcome FEV_1 and especially lower outcome $\dot{V}max_{50}$ than did those in the 3 other groups; the trends in their function were not linear, and these values after 20 yr of age were still below normal. Those who developed asthma during the study had lower outcome $\dot{V}max_{50}$ (but not FEV_1) than did those who never had asthma or remit-

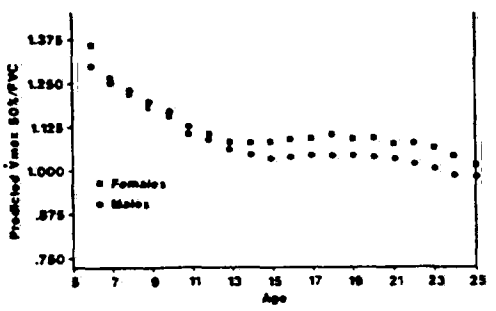

Fig. 2. Predicted $\dot{V}max_{50}/FVC$ by age and sex (details and formulas in text).

ted. Those who remitted from asthma or chronic bronchitis during the study had end-point function between those who continued to have it and those who never had it. Outcome function in different asthma histories was significantly related to age of onset (in bivariate ANOVAs only), especially $\dot{V}max_{50}$ in those with "always asthma": mean outcome residuals were −31.2 for onsets < 5 yr and −16.0 for onsets ≥ 5 yr. As average age of new onsets was significantly different also (6.9 yr versus 3.1 yr for others), outcome $\dot{V}max_{50}$ was adjusted for age (as seen in table 3). Sex and other factors were not significant covariates in effects of diagnosis on function.

After symptoms, smoking habits had an important effect on outcome. Residuals were significantly affected by smoking habits, both before and after adjusting for other factors (by multifactor analyses of variance). The outcomes were related to symptoms within smoking groups, as shown for FEV_1 and $\dot{V}max_{50}$ (table 4); after adjustment for other factors, symptoms were related still to outcome $\dot{V}max_{50}$. Sex was a significant covariable in this multivariate relationship. The interaction between smoking and symptoms was significant for both outcomes, and those who both smoked and had symptoms had the lowest end-point residuals (table 4). The number of observations per individual subject, used as a covariable, was not significant. Parental airway obstructive diseases (diagnosed emphysema, chronic bronchitis, or asthma) had additional effects with children's smoking and symptoms for end-point $\dot{V}max_{50}$, but not independently; the residual for current smokers with symptoms and parental history was −14.41 (95% confidence interval of −4.57 to −24.25).

Parental smoking was not significant as a main effect within the multifactor analysis of variance for outcome FEV_1 or $\dot{V}max_{50}$. However, it showed a significant interaction with subjects' smoking (children smoked if parents did) and parental AOD in its effects on $\dot{V}max_{50}$ (table 5). There were no such associations in subjects whose parents did not have AOD (not shown). Maternal smoking is significantly related to FVC ($p < 0.001$), producing a positive FVC residual: +3.13 versus −1.48 using sex-specific equations and +3.29 versus −1.36 using combined gender equations. This "inverse" relationship is found in all age groups, but is significant primarily in the older age groups and in females.

TABLE 2

ALL RESIDUALS OF $\dot{V}max_{50}$ BY SYMPTOMS BY AGE GROUP*

	AGE (yr)					
Ever Had Sx	All†	5.5–10	11–15	16–20	21–25	Total Yes (%)
Cough	−4.84	+0.51	−3.61	−6.34	−5.69	23.9
No	+1.43					
Phlegm	−7.20	−1.93	−10.07	−5.47	−8.42	15.8
No	+1.27					
Wheeze	−5.80	−6.88	−5.11	−5.81	−6.12	14.2
No	+2.83					
Attacks sob wheeze	−8.51	−6.22	−8.91	−10.44	−6.17	13.9
No	+1.46					
Any asthma	−13.58	−17.97	−13.95	−10.80	−15.69	7.4
No	+1.26					

* ANOVA, YES versus NO; $p < 0.001$ for Yes versus No

† The number of observations (persons times tests, for persons with 3+ tests) = 1,487

TABLE 3

OUTCOME FEV_1 AND $\dot{V}max_{50}$ RESIDUALS BY PHYSICIAN CONFIRMED ASTHMA: CHILDREN ≤ 14 YEARS OF AGE

		FEV_1		$\dot{V}max_{50}$ (unadjusted)		$\dot{V}max_{50}$ (adjusted)†
	Number	Mean	SD	Mean	SD	Mean
MD asthma						
Always	9	−6.94	11.05	−24.49	19.20	−24.8
New	24	−0.69	18.74	−16.19	20.15	−20.9
Remission	17	−0.77	16.04	−1.97	29.71	+1.37
Never	390	+3.02	13.37	+1.69	25.13	
Overall (ANOVA)			$p = 0.07$		$p < 0.0002$	$p < 0.05$
Any asthma outcome		−2.36	$p = 0.03$	−17.43	$p < 0.0001$	

* Adjusted values for age and asthma groups only. There were significantly different means by age of onset (< 5 versus > 5) and significantly different age of onset of new cases: 6.9 ± 5.8 versus 3.1 ± 2.7 for "always" and "remissions" ($p < 0.008$); so means were adjusted for age by ANOVA. age of onset was not a significant main or interactive effect in overall ANOVA values. Sex was adjusted for, though not a significant covariable, because of slight differences in trends

TABLE 4

OUTCOME FEV_1 AND $\dot{V}max_{50}$ RESIDUALS BY CHILDREN'S SMOKING AND SYMPTOMS: CHILDREN ≤ 14 YEARS OF AGE AT ENTRY (n = 237)*

	Smoking						
	FEV_1			$\dot{V}max_{50}$			
Symptoms	Current	Ex	Never	Current	Ex	Never	Adjusted†
Ever	−2.77	−1.59	2.48	−12.12	−4.69	0.10	−4.33
Never	1.26	13.08	2.71	−1.90	8.93	3.66	2.43
	$p < 0.02$			$p < 0.04$			
Adjusted†	−1.49	6.83	2.86	−7.44	−0.04	2.85	

* Reduced N related to availability of information on all variables. All p values by ANOVA

† For FEV_1, adjusted for symptoms, passive smoking, parents' AOD, and age group (all ns), and sex (significant) in ANOVA $p \leq 0.077$ for adjusted smoking; significant interactions of smoking with symptoms ($p = 0.044$). For $\dot{V}max_{50}$, adjusted main effects for each other, age, sex, parents' AOD and smoking, and number of observations (all ns) in ANOVA; $p < 0.031$ for adjusted smoking and $p \geq 0.044$ for adjusted symptoms.

For size-compensated flows ($\dot{V}max_{50}$/FVC), females had higher predicted values between ages 13 and 25 (figure 2). Size compensation removed any further effects of age on residuals. Subjects' symptoms were still highly correlated with the outcome residuals (table 6), regardless of gender. There was a significant relationship for subjects' smoking with outcome residuals, using sex-specific or combined models. (The effect of ever smoking was seen more in those 15 to 25 yr of age at end point.) Parental smoking was not significant, though smoking habits of mothers showed a trend. (Maternal smoking was significant independently ($p \leq 0.012$) only when all observations were evaluated together.) There were no significant interactions in the multifactor ANOVA.

TABLE 5

OUTCOME $Vmax_{50}$ RESIDUALS BY CHILDREN'S SMOKING*, PARENT'S SMOKING, AND PARENTS' AOD† CHILDREN ⩽ 14 YEARS OF AGE AT ENTRY‡

	Total¶		Parents with AOD	
Smoking	Current	Never	Current	Never
Parents' Smoking				
Mother§	−9.13‖	4.48	−9.09	2.36
Father only	−5.73	1.28	−3.23	−11.04
Father§	−7.07	0.71	−6.53	−7.00
Neither	−0.40	5.86	0.25	13.88
ANOVA (vs neither)	Mother§ and father only ns. Father§, $p \leqslant 0.03$		ns $\leqslant 0.06$	

* Ex-smokers not shown.
† As diagnosed emphysema, chronic bronchitis, or asthma.
‡ Ages 12.4 to 28.4 yr at end point.
¶ Reduced N related to availability of information on all variables and age (170).
§ ♂/♀ spouse smoking.
‖ 95% confidence interval is −1.85 to −16.41, all others encompass 0.

TABLE 6

OUTCOME $Vmax_{50}$/FVC RESIDUALS RELATED TO CHILDREN'S SMOKING AND SYMPTOMS, AND PARENTAL SMOKING ($n = 389$): CHILDREN ⩽ 14 YEARS OF AGE AT ENTRY

Adjusted Independent Factors*	Adjusted Means	p Values
Subjects' symptoms		
Yes	−3.24	
No	−0.67	< 0.014
Subjects' smoking		
Ever	−10.02	
Never	−1.25	⩽ 0.013
Mothers' smoking†		
Current	−4.41	
Ex	−3.61	
Never	−0.40	⩾ 0.42
Overall ANOVA		< 0.001

* These main effects adjusted for sex ($p < 0.001$), age (ns), and each other; fathers' smoking removed (as inconsistent trend).
† Adjusted for fathers' smoking as well.

TABLE 7

INDIVIDUAL GROWTH RATES* OF FEV, AND $Vmax_{50}$ BY RISK FACTORS,† COVARIABLES,‡ AND INDIVIDUAL VARIABILITY§

	Number¶	Adjusted FEV_1	Adjusted $Vmax_{50}$
Smoking			
Current	52	0.74	0.65
Ex	20	0.85	0.92
Never	137	0.83	0.93
		$p = 0.055$	$p = 0.005$
Symptoms			
Yes	(79)	–	0.74
No	(130)	–	0.93
		ns	$p = 0.014$

* Coefficient of (age × ht²) × 1,000.
† Smoking and symptoms adjusted for each other as well as the other factors (including parental smoking, which was not significant).
‡ Age and sex (significant).
§ Using SEE (correlated with # tests and age, not with risk factors), and number of observations. (Correlated with age, years of follow-up, and with unadjusted FEV_1.)
¶ Reduced because of lack of data on individual smoking (e.g., ages under 15 yr) or symptoms.

The use of the repeated measures ANOVA linear model confirmed the findings posited. Thus, residuals from the fitted developmental curves analyzed by multifactorial ANOVA/ANCOVA "fit" the more general linear model.

Results of Individual Development Model

As previously stated, individual "growth" rates ("slopes") were evaluated following the approach of Goldstein (21, 22), using multifactorial analysis of covariance. Standard errors of estimate (SEE) were used as a covariate for individual variability (within and between surveys). The SEE were significantly correlated with the number of tests and age, but not with any of the risk factors. The number of observations per individual was used as a covariable also. It was correlated with age (and, of course, years of follow-up). It was correlated significantly with unadjusted mean FEV_1 in the different surveys, though without trend, indicating random survey differences. The individual "slopes" were not correlated with initial values, but were correlated with end-point (final follow-up) values. After each explanatory variable was adjusted for covariables and other explanatory variables, only symptoms and smoking were highly related to individual slopes, especially those of $Vmax_{50}$ (table 7).

Discussion

The composite unweighted method was used to obtain the best descriptive fit for lung function development (i.e., growth) curves. It was not developed only to look for deviations/variations from time trends, as with time series models. The method used was found to be very robust. It adjusted for age and for body size (standing height), after which other measurements (sitting height, arm span) did not contribute to explaining functional measurements. Unfortunately, we did not make chest measurements, which have been found to help explain the growth curve in late adolescence and early twenties (8). The method is not intended as a reference formula. It is the mathematical best fit to the data and is not assumed to adequately describe biologic growth, although the solutions parallel our previous descriptive results (18).

The method provided very similar results for those with different numbers of observations, as long as subjects have 3 or more observations over an 8- to 12-yr period. Individuals with only 2 points do not provide sufficient information and do not fit the curvilinear solutions. Over lengthy time periods, observations on an individual subject appear to be distributed over the entire age range, thus minimizing dependency of observations. (Thus, there were no major losses of degrees of freedom or increased inter-

dependence of the observations based on the number of values used for an individual subject.) We used values that could be examined at the follow-up end point and at onset. The use of residuals was very convenient statistically in that it led to variables that were approximately normally distributed, around a zero average, and was equivalent to looking at percentages above normal and percentages below normal in evaluating other factors affecting the development curve.

The use of the repeated measures ANOVA linear model (19, 20) as an adjunct to the composite-residual method showed that the descriptive fit, used for physiologic purposes/results yielded a good fit to a general linear model. The use of ANOVA/ANCOVA to analyze differences, as per Ware and coworkers (9), was a very robust and pragmatic approach. Results that can be provided as actual decrements of function are far more understandable than are odds ratios or chi-square results.

Residuals were used to examine the phenomena of "tracking" the subjects' values over time. Thus, the relation of each one to "average" growth in this population was evaluated by looking at any change in the relation of the deviations from average (i.e., these residuals) over time. Normal subjects showed negligible mean change in their residuals from initial to end point per annum. The grand mean change in residuals was only 0.26%, even including those with symptoms, smoking, and other risk factors. Only active smoking disturbed the tracking with any significance ($p = 0.099$), with current smokers having an adjusted mean change of -0.64%. Symptoms, often present initially, only produced a -0.19% change ($p = 0.17$). Other factors had no apparent influence on tracking.

The number of observations related signi[illegible]cantly but without pattern only to survey. In all methods of analysis, the number of observations was used as a covariate as a measure of individual variability; its lack of significant contributions was considered another indication of the strength of this approach to modeling. The SEE derived for each subject with ≥ 3 values represents a measure of within-individual variability. It was found to be unrelated to any risk variables, and related only to age and the number of observations. The SEE was used as a covariate in analyses of growth rates (individual "slopes"), using a linear model after the fashion of Goldstein (21, 22), to determine contributions of risk variables to changes over time. The results therefrom substantiated previous results, as well as providing another measure of outcome.

Size-compensated flows (expressing $\dot{V}max_{50}$ in FVC seconds) showed the same pattern with age and by sex (figure 2) as shown in infants and smaller children (10, 23); females had higher flows for given volumes than did males after puberty, even though males had higher volumes. For size-compensated flows, sex-specific analysis yielded the same results as those obtained for the combined group using gender as a covariable. Flows per se ($\dot{V}max_{50}$) did not differ significantly by gender. As discussed by us previously (10, 14–18, 23) and by others (3, 8, 11), the FEV_1 and flows do measure airway and parenchymal changes, and one can discriminate differential contributions, especially when evaluating flow as a ratio to vital capacity.

Symptomatology contributed as well to outcome function as another predictor of risk, but not to individual rates of growth. Outcome function, of course, was very well correlated with outcome symptomatology as well, and to individual growth rates. Outcomes related specifically to incidence and remission of asthma and chronic bronchitis. As shown by others (11), abnormalities of flow (i.e., the $\dot{V}max_{50}$) persist longer, into adulthood.

Further, children's symptomatology (by parental response and self response) was related to parental history of AOD. The latter did relate to outcome of symptomatology, and it modified effects of other factors (see below). Initial measured pulmonary function was influenced by both parental factors and the children's respiratory history, and growth in function was affected by these factors, the level of their initial function, and later symptomatology. This information confirms longitudinally, in a preliminary fashion at least, that our hypotheses that childhood respiratory trouble, effects of key respiratory illness, and the effects of parental/familial factors are all important in growth of pulmonary function in children (24–26).

Smoking had a major effect on growth of pulmonary function as well, and there was an interaction of smoking habits of the subjects and symptomatology on outcome of pulmonary function. Ex-smokers may have shown a rebound phenomenon, seen in analyses of young adults (27). Children appear to smoke in part because parents do. As found by many others, there was a significant relationship between the smoking habits of parents and those of their children, especially between those of the same gender. Likewise, mothers and fathers who smoked usually had spouses who smoked.

Further, parental smoking had an influence on the children's pulmonary function outcome. It was most evident in current smokers, symptomatic subjects, and those with a parental history of AOD. Mothers' smoking was significant, as found by others (9, 28), but we also found fathers' smoking to be important. Parental smoking did not influence height at any age, as suggested by these previous studies. We found that subjects did have increased volumes (FVC) and decreased flows if parents smoked. The effect did not differ by gender and was noted even in 5 to 7-yr-olds, although the magnitude was greater in older children and young adults. It is interesting that preliminary studies on infants (29) suggest that children of smoking mothers, especially males, may have elevated functional residual capacities even shortly after birth. We have observed also that adult male smokers who show a rapid subsequent functional decline are likely to have well-preserved FVC values at an early stage of their illness (30). The mechanism underlying these observations remains unclear, but it would appear that an increase in lung volume could be an early manifestation of the effects of active or even passive smoking, related to stimulation effects of nicotine, or growth compensatory effects related to CO exposure and/or possible loss of lung elasticity.

Our robust method of lung function growth showed effects on function of various risk factors that are highly compatible with those seen using the traditional general mixed linear model and additional linear model of individual growth (21, 22). Thus, the linear models used are consistent in this population in reflecting actual growth of pulmonary function and the factors that affect it.

In conclusion, pulmonary function growth is significantly related to children's respiratory symptoms and disease, and their smoking; parental/familial factors are important in some subgroups as well. Surprisingly, symptoms/disease are not integral in analyses in other studies (9, 28), nor are the interactions of important risk factors. The effects of parental smoking are somewhat inconsistent; in some cases a maternal smoking

effect is noted only within other risk factor subgroups. The independent and interactive effects are seen as perturbations in the growth curve as well as in outcome function (FVC, FEV_1, $\dot{V}max_{50}$, $\dot{V}max_{50}$/FVC). Flows ($\dot{V}max_{50}$) and size-compensated flows ($\dot{V}max_{50}$/FVC) were the most sensitive, and often showed persistence of decrement related to early events.

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